



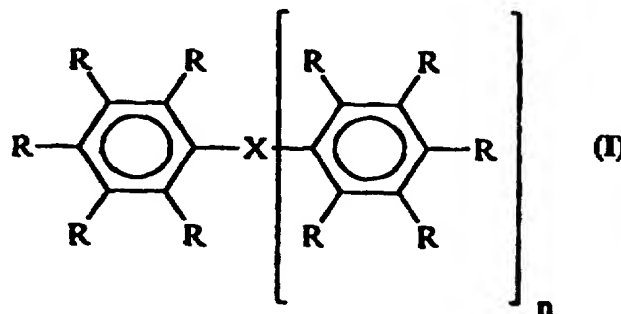
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(54) Title: IODINATED X-RAY CONTRAST MEDIA

## (57) Abstract

The invention provides low viscosity iodinated aryl compounds, useful as X-ray contrast agents, of formula (I), wherein n is 0 or 1, and where n is 1 each C<sub>6</sub>R<sub>5</sub> moiety may be the same or different; each group R is a hydrogen atom, an iodine atom or a hydrophilic moiety M or M<sub>1</sub>, two or three non-adjacent R groups in each C<sub>6</sub>R<sub>5</sub> moiety being iodine and at least one, and preferably two or three, R groups in each C<sub>6</sub>R<sub>5</sub> moiety being M or M<sub>1</sub> moieties; X denotes a bond or a group providing a 1 to 7 atom chain linking two C<sub>6</sub>R<sub>5</sub> moieties or, where n is 0, X denotes a group R; each M independently is a non-ionic hydrophilic moiety; and each M<sub>1</sub> independently represents a C<sub>1-4</sub>alkyl group substituted by at least one hydroxyl group and optionally linked to the phenyl ring via a carbonyl, sulphone or sulfoxide group, at least one R group being an M<sub>1</sub> moiety; with the proviso that where n is zero either at least one M<sub>1</sub> group other than a hydroxymethyl or 1,2-dihydroxyethyl group is present or then if one hydroxymethyl or 1,2-dihydroxyethyl M<sub>1</sub> group is present at least one nitrogen-attached or hydroxylated-C<sub>3-4</sub> alkyl moiety-containing M group is also present and isomers thereof.



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### Iodinated X-ray contrast media

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This invention relates to improvements in and relating to contrast media, and in particular iodinated X-ray contrast media.

Contrast media may be administered in medical  
10 imaging procedures, for example X-ray, magnetic resonance and ultrasound imaging, to enhance the image contrast in images of a subject, generally a human or non-human animal body. The resulting enhanced contrast enables different organs, tissue types or body  
15 compartments to be more clearly observed or identified. In X-ray imaging, the contrast media function by modifying the X-ray absorption characteristics of the body sites into which they distribute.

Clearly however the utility of a material as a  
20 contrast medium is governed largely by its toxicity, by its diagnostic efficacy, by other adverse effects it may have on the subject to which it is administered, and by its ease of storage and ease of administration.

Since such media are conventionally used for  
25 diagnostic purposes rather than to achieve a direct therapeutic effect, when developing new contrast media there is a general desire to develop media having as little as possible an effect on the various biological mechanisms of the cells or the body as this will  
30 generally lead to lower animal toxicity and lower adverse clinical effects.

The toxicity and adverse biological effects of a contrast medium are contributed to by the components of the medium, e.g. the solvent or carrier as well as the  
35 contrast agent and its components (e.g. ions where it is

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ionic) and metabolites.

The following major contributing factors to contrast media toxicity and adverse effects have been identified:

5

- the chemotoxicity of the contrast agent,
- the osmolality of the contrast medium, and
- the ionic composition (or lack thereof) of the contrast medium.

10

In coronary angiography, for example, injection into the circulatory system of contrast media has been associated with several serious effects on cardiac function. These effects are sufficiently severe as to place limitations on the use in angiography of certain contrast media.

15

In this procedure, for a short period of time a bolus of contrast medium rather than blood flows through the circulatory system and differences in the chemical and physicochemical nature of the contrast medium and the blood that it temporarily replaces can give rise to undesirable effects, e.g. arrhythmias, QT-prolongation, and, especially, reduction in cardiac contractile force and occurrence of ventricular fibrillation. There have been many investigations into these negative effects on cardiac function of infusion of contrast media into the circulatory system, e.g. during angiography, and means for reducing or eliminating these effects have been widely sought.

20

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Early injectable ionic X-ray contrast agents, based on triiodophenylcarboxylate salts, were particularly associated with osmotoxic effects deriving from the hypertonicity of the contrast media injected.

30

This hypertonicity causes osmotic effects such as the draining out of water from red-blood cells, endothelial cells, and heart and blood vessel muscle cells. Loss of water makes red blood cells stiff and hypertonicity, chemotoxicity and non-optimal ionic make-

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up separately or together reduce the contractile force of the muscle cells and cause dilation of small blood vessels and a resultant decrease in blood pressure.

5 The osmototoxicity problem was addressed by the development of the non-ionic triiodophenyl monomers, such as iohexol, which allowed the same contrast effective iodine concentrations to be attained with greatly reduced attendant osmototoxicity effects.

10 The drive towards reduced osmototoxicity led in due course to the development of the non-ionic bis(triiodophenyl) dimers, such as iodixanol, which reduce osmototoxicity associated problems still further allowing contrast effective iodine concentrations to be achieved with hypotonic solutions.

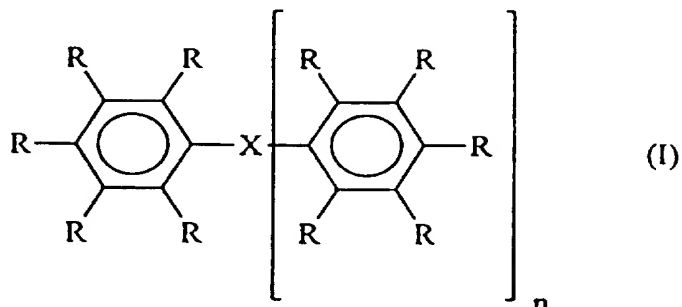
15 This ability to achieve contrast effective iodine concentrations without taking solution osmolality up to isotonic levels (about 300mOsm/kg H<sub>2</sub>O) further enabled the contribution to toxicity of ionic imbalance to be addressed by the inclusion of various plasma cations, as  
20 discussed for example in WO-90/01194 and WO-91/13636 of Nycomed Imaging AS.

However X-ray contrast media, at commercial high iodine concentrations of about 300 mgI/ml, have  
25 relatively high viscosities, ranging from about 15 to about 60 mPas at ambient temperature with the dimeric media generally being more viscous than the monomeric media. Such viscosities pose problems to the administrator of the contrast medium, requiring  
30 relatively large bore needles or high applied pressure, and are particularly pronounced in paediatric radiography and in radiographic techniques which require rapid, bolus administration, e.g. in angiography.

The present invention addresses the viscosity problem encountered with the prior art materials and  
35 thus viewed from one aspect the invention provides

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iodinated aryl compounds, useful as X-ray contrast agents, of formula I



(wherein n is 0 or 1, and where n is 1 each C<sub>6</sub>R<sub>5</sub> moiety may be the same or different; each group R is a hydrogen atom, an iodine atom or a hydrophilic moiety M or M<sub>1</sub>, two or three non-adjacent R groups in each C<sub>6</sub>R<sub>5</sub> moiety being iodine and at least one, and preferably two or three, R groups in each C<sub>6</sub>R<sub>5</sub> moiety being M or M<sub>1</sub> moieties; X denotes a bond or a group providing a 1 to 7, for example 1, 2, 3 or 4 atom chain linking two C<sub>6</sub>R<sub>5</sub> moieties or, where n is 0, X denotes a group R; each M independently is a non-ionic hydrophilic moiety; and each M<sub>1</sub> independently represents a C<sub>1-4</sub>alkyl group substituted by at least one hydroxyl group and optionally linked to the phenyl ring via a carbonyl, sulphone or sulfoxide group, at least one R group, preferably at least two R groups and especially preferably at least one R group in each C<sub>6</sub>R<sub>5</sub> moiety, being an M<sub>1</sub> moiety; with the proviso that where n is zero either at least one M<sub>1</sub> group other than a hydroxymethyl or 1,2-dihydroxyethyl (and optionally other than any hydroxyethyl) group is present or then if one hydroxymethyl or 1,2-dihydroxyethyl M<sub>1</sub> group (and optionally any hydroxyethyl group) is present at least one nitrogen-attached hydroxylated alkyl (preferably C<sub>1-4</sub>-alkyl) moiety-containing M group is also present) and isomers, especially stereoisomers and rotamers, thereof.

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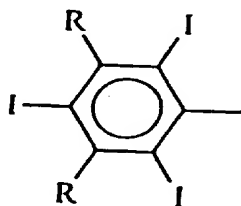
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It is found that the compounds of the invention exhibit advantageously low viscosity in aqueous solution; this is thought to derive from the presence of  $M_1$  groups on the phenyl groups, from compound asymmetry and, in the dimer compounds, from the nature of the linker X (especially where X provides a linkage less than 5 atoms in length).

Thus for example all of the water-soluble monomer compounds according to the invention that have been tested have exhibited viscosities lower than that of iohexol.

The compounds of formula I are preferably asymmetric. For the monomer compounds (where  $n = 0$ ) this may be achieved by asymmetric substitution of the phenyl ring. For the dimers this can be achieved by the use of an asymmetric 2 or more atom chain-forming group X and/or by selection of non-identical  $C_6R_5$  groups, i.e. by non-identical substitution of the iodophenyl end groups. Asymmetric molecules are preferred as they have been found to have better water-solubility.

Such non-identical substitution of the phenyl end groups, the  $C_6R_5$  moieties, may be achieved by having different numbers or positions of iodine substitution and/or by different numbers, positions or identities of M or  $M_1$  substitution. To maximize iodine loading, triiodophenyl end groups, i.e. groups of formula

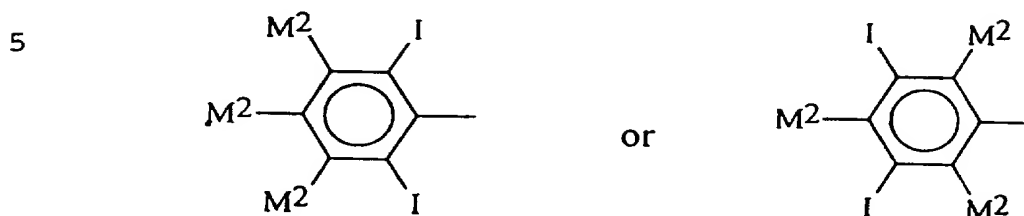


are preferred, and in these the two R groups may be the same or different, although preferably both represent M

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or  $M_1$  groups.

Where a phenyl end group is disubstituted by iodine, it is preferably of formula



(where each  $M^2$  may be the same or different and represents an  $M_1$  or  $M$  group, at least one on each ring preferably representing an  $M_1$  group).

Generally, diiodophenyl-diiodophenyl dimers will be  
 15 less preferred than the diiodophenyl-triiodophenyl or triiodophenyl-triiodophenyl dimers, due primarily to their reduced iodine loading, i.e. 4 rather than 5 or 6 iodines per dimer molecule. Indeed the triiodophenyl-triiodophenyl dimers are generally preferred due to  
 20 their higher iodine loading.

For the monomers, the triiodophenyl compounds are again preferred.

The solubilizing groups  $M$  may be any of the non-ionizing groups conventionally used to enhance water  
 25 solubility. Suitable groups include for example straight chain or branched  $C_{1-10}$ -alkyl groups, preferably  $C_{1-5}$  groups, optionally with one or more  $CH_2$  or  $CH$  moieties replaced by oxygen or nitrogen atoms and optionally substituted by one or more groups selected  
 30 from oxo, hydroxy, amino, carboxyl derivative, and oxo substituted sulphur and phosphorus atoms. Particular examples include polyhydroxyalkyl, hydroxyalkoxyalkyl and hydroxypolyalkoxyalkyl and such groups attached to the phenyl group via an amide linkage such as  
 35 hydroxyalkylaminocarbonyl,  $N$ -alkyl-hydroxyalkylaminocarbonyl and bis-hydroxyalkylaminocarbonyl groups. Preferred among such



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groups are those containing 1, 2, 3, 4, 5 or 6, especially 1, 2 or 3, hydroxy groups, e.g.

- CONH-CH<sub>2</sub>CH<sub>2</sub>OH
- 5    -CONH-CH<sub>2</sub>CHOHCH<sub>2</sub>OH
- CONH-CH(CH<sub>2</sub>OH)<sub>2</sub>
- CON(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>
- as well as other groups such as
- CONH<sub>2</sub>
- 10    -CONHCH<sub>3</sub>
- OCOCH<sub>3</sub>
- N(COCH<sub>3</sub>)H
- N(COCH<sub>3</sub>)C<sub>1-3</sub>-alkyl
- N(COCH<sub>3</sub>)-mono, bis or tris-hydroxy C<sub>1-4</sub>-alkyl
- 15    -N(COCH<sub>2</sub>OH)-mono, bis or tris-hydroxy C<sub>1-4</sub>-alkyl
- N(COCH<sub>2</sub>OH)<sub>2</sub>
- CON(CH<sub>2</sub>CHOHCH<sub>2</sub>OH)(CH<sub>2</sub>CH<sub>2</sub>OH)
- CONH-C(CH<sub>2</sub>OH)<sub>3</sub> and
- CONH-CH(CH<sub>2</sub>OH)(CHOHCH<sub>2</sub>OH).

20

In general, the M groups will preferably each comprise a polyhydroxy C<sub>1-4</sub>-alkyl group, such as 1,3-dihydroxyprop-2-yl or 2,3-dihydroxyprop-1-yl.

- 25    Other such M groups as are conventional within the field of triiodophenyl X-ray contrast agents may also be used and the introduction of M groups onto iodophenyl structures may be achieved by conventional techniques.

- 30    In general, M<sub>1</sub> groups preferably comprise C<sub>1-4</sub>-alkyl groups substituted by 1, 2, 3 or 4 hydroxy groups (e.g. hydroxymethyl, 2-hydroxyethyl, 2,3-bishydroxypropyl, 1,3-bishydroxyprop-2-yl, 2,3,4-trihydroxybutyl, and 1,2,4-trihydroxybut-2-yl) optionally connected to the phenyl ring via a CO, SO or SO<sub>2</sub> group (e.g. COCH<sub>2</sub>OH or SO<sub>2</sub>CH<sub>2</sub>OH).

- 35    In the dimeric compounds of the invention, the linker group X is conveniently a bond or a 1 to 7, eg 1,

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2, 3 or 4, membered chain comprising carbon, nitrogen, oxygen or sulphur atoms, e.g.

a bond,

a O, S, N or C one atom chain,

5 a NN, NC, NS, CC or CO two atom chain,

or a NCN, OCN, CNC, OCO, NSN, CSN, COC, OCC or CCC three atom chain,

for example:

an oxygen atom or a group  $\text{NR}^1$ , CO,  $\text{SO}_2$  or  $\text{CR}_2^1$ ;

10 a group COCO,  $\text{CONR}^1$ ,  $\text{COCR}_2^1$ ,  $\text{SOCR}_2^1$ ,  $\text{SO}_2\text{NR}^1$ ,  $\text{CR}_2^1\text{CR}_2^1$ ,  $\text{CR}_2^1\text{NR}^1$  or  $\text{CR}_2^1\text{O}$ ;

a group  $\text{NR}^1\text{CONR}^1$ ,  $\text{OCONR}^1$ ,  $\text{CONR}^1\text{CO}$ ,  $\text{CONR}^1\text{CR}_2^1$ ,  $\text{OCOO}$ ,  $\text{CR}_2^1\text{OCR}_2^1$ ,  $\text{OCR}_2^1\text{CO}$ ,  $\text{CR}_2^1\text{CONR}^1$ ,  $\text{CR}_2^1\text{CR}_2^1\text{CR}_2^1$ ,  $\text{COCR}^1\text{R}^1\text{CO}$ ,  $\text{CR}_2^1\text{NR}^1\text{CR}_2^1$ ,  $\text{CR}_2^1\text{SO}_2\text{NR}^1$ ,  $\text{CR}_2^1\text{OCO}$  or  $\text{NR}^1\text{SO}_2\text{NR}^1$ ;

15 where  $\text{R}^1$  is hydrogen or a  $\text{C}_{1-6}$ -alkyl or alkoxy group optionally substituted by hydroxy, alkoxy, oxa or oxo (e.g. a polyhydroxyalkyl, formyl, acetyl, hydroxyl, alkoxy or hydroxyalkoxy group) and where it is attached to a carbon atom  $\text{R}^1$  may also be a hydroxyl group.

20 When X provides a 4-7 atom linkage, conventional linker groups, such as for example those suggested by Justesa in WO-93/10078 or Bracco in US-A-4348377 and WO-94/14478 may be used.

In general such linkages will comprise optionally  
25 aza or oxa substituted alkylene chains optionally carrying  $\text{R}^1$  substituents, especially such groups terminating with imine nitrogen or, more preferably, carbonyl carbon atoms, preferably belonging to iminocarbonyl functional units within the chain.

30 Hydroxylated chains, such as are found in iodixanol are particularly preferred.

Examples of such chains are NCCN, NCCCN, CNCCCNC, and CNCCN, eg.

35  $-\text{NR}^1\text{COCONR}^1-$

$-\text{NR}^1\text{COCR}_2^1\text{CONR}^1-$

$-\text{NR}^1\text{CR}_2^1\text{CR}^1\text{OHCR}_2^1\text{NR}^1-$

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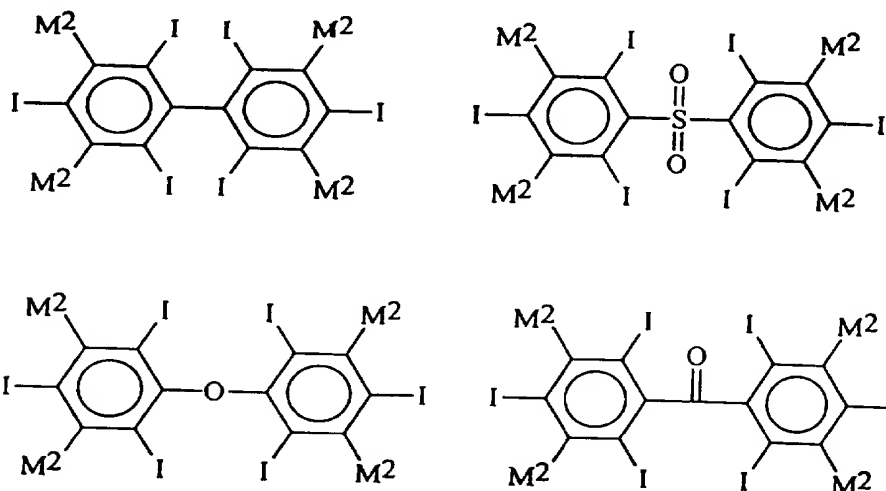
$-\text{CONR}^1\text{CR}^1_2\text{CONR}^1-$  and

$-\text{N}(\text{COR}^1)\text{CR}^1_2\text{CR}^1\text{OHN}(\text{COR}^1)-$ ,

eg as found in iotrolan, iofratol, ioxaglic acid and iodixanol, or as otherwise indicated in WO-94/14478.

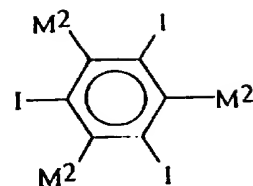
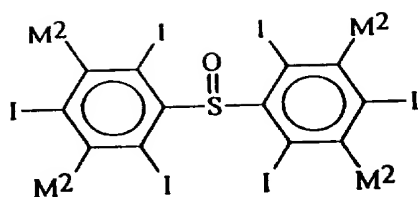
5           Advantageously, in the dimer compounds the X group is not symmetrical. This may be achieved for example by asymmetrical substitution of a symmetrical chain (e.g. N-C-N substituted as  $\text{NHCONR}^1$ ) or by selection of an asymmetric chain (e.g. OCN substituted as  $\text{OCONR}^1$ ). In  
10           particular, it is preferred that the linker group X should be polar and also that it should be hydrophilic.

          Thus examples of preferred structures according to the invention include:

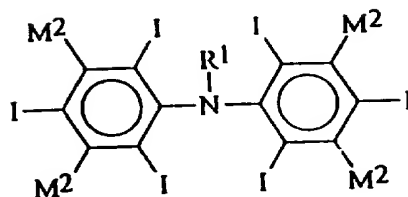
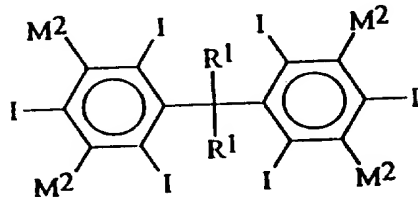


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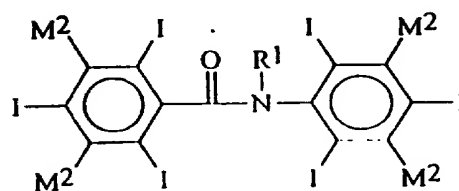
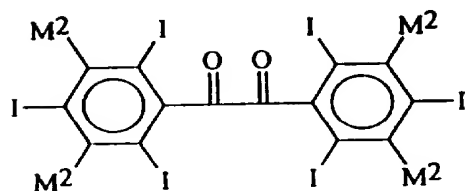
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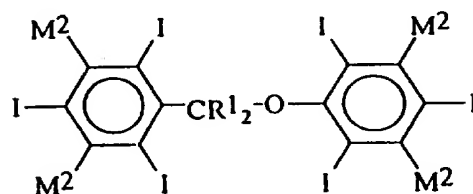
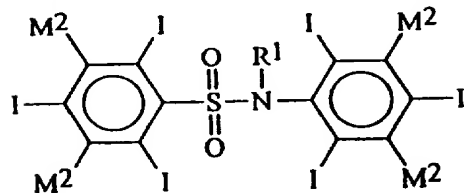
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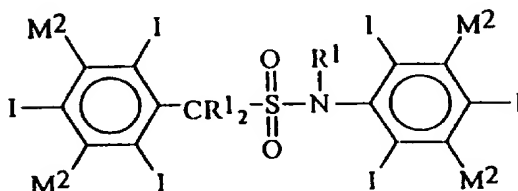
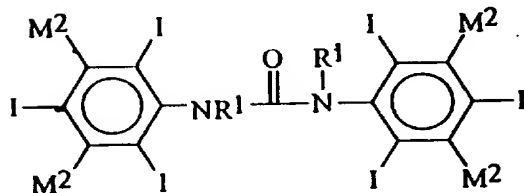
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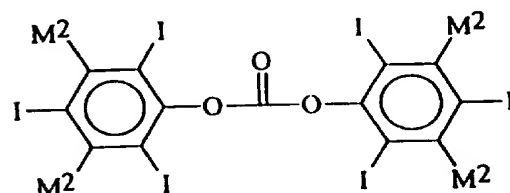
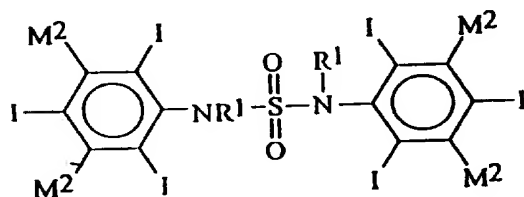
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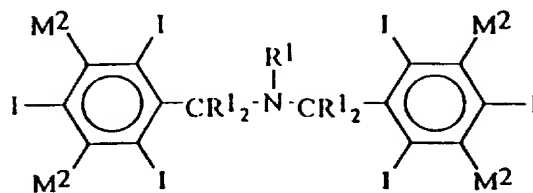
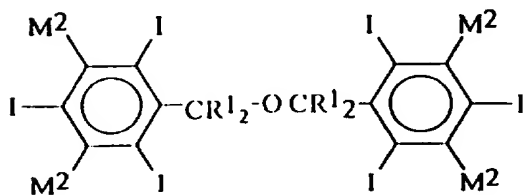
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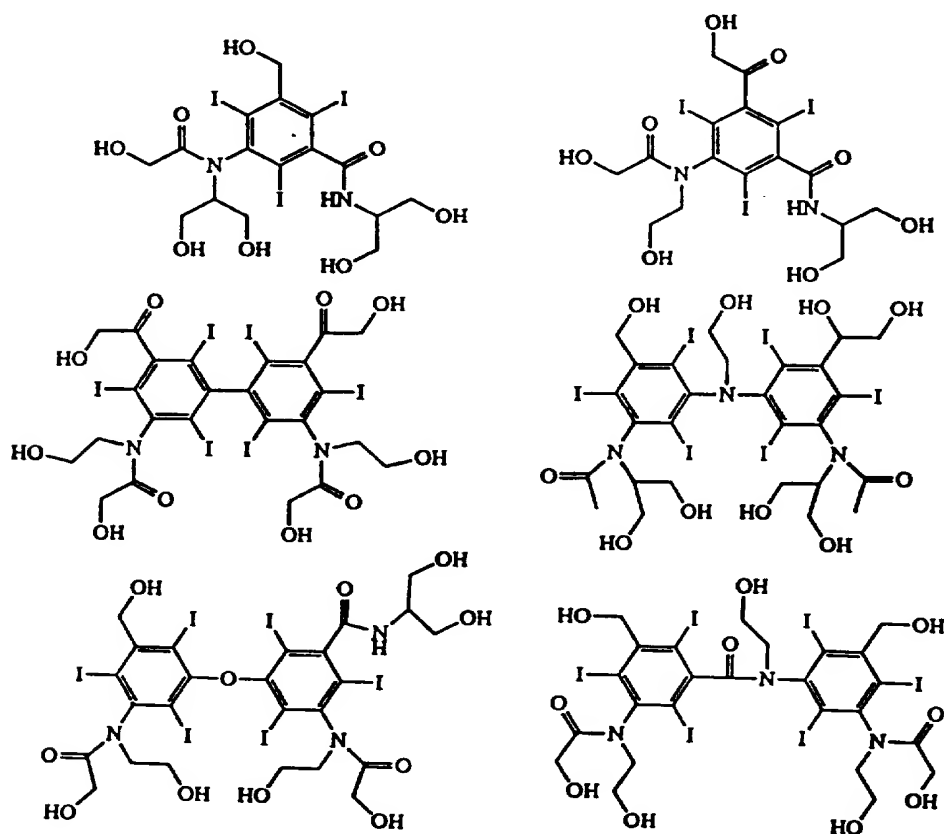
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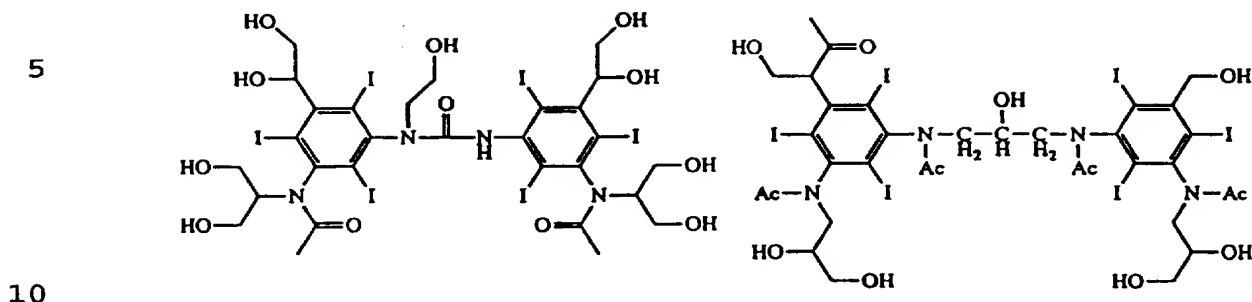
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where each  $M^2$  is  $M_1$  or  $M$ , at least one in each compound (and preferably on each ring) being  $M_1$ , especially where at least one  $M^2$  is a  $C_{1-4}$ -alkyl group substituted by 1, 2, 3 or 4 hydroxy groups (e.g. hydroxymethyl, 2-hydroxyethyl, 2,3-bishydroxy-propyl, 1,3-bishydroxyprop-2-yl, 2,3,4-trihydroxybutyl, and 1,2,4-trihydroxybut-2-yl) optionally connected to the phenyl ring via a CO, SO or  $SO_2$  group (e.g.  $COCH_2OH$  or  $SO_2CH_2OH$ ), e.g. a hydroxyalkyl or hydroxyalkylcarbonyl group, in particular a hydroxymethyl, hydroxymethylcarbonyl, 2-hydroxyethyl or 2-hydroxyethylcarbonyl group, and where  $R^1$  is hydrogen, hydroxyl, hydroxyalkyl (e.g. 2-hydroxyethyl), acetyl or hydroxyalkylcarbonyl.

Particular preferred compounds are those of formula



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The compounds of the invention may in general be prepared in two or three stages: (a) dimer formation (where necessary), (b) iodination of phenyl groups and (c) substitution of phenyl groups and/or optionally linker moieties by solubilizing moieties.

While, in theory, stages (a), (b) and (c) can be performed in any order, it will generally be preferred to perform the dimer formation step before the iodination step and, for reasons of economy, it will be preferred to perform the iodination step at as late a stage in the synthesis as is feasible so as to reduce iodine wastage. The dimer formation stage may itself be a multi-step procedure with an appropriate activated linker first being attached to one monomer before the resulting linker-monomer conjugate is reacted with a second monomer. Alternatively, dimer formation may be by way of reaction of similarly or cooperatively substituted monomers with the conjugation of the monomers leading to dimer formation.

Where desired the linker group X may be produced by modification, e.g. substitution, oxidation or reduction, of a precursor linker, e.g. in a precursor monomer.

For the monomer compounds, especially those where ring substitution is asymmetric, iodine loading will generally be effected before or after partial

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substitution of the phenyl ring with R groups.

In all cases, conventional synthetic routes wellknown in the literature (eg methods analogous to those used and described for the production of the compounds referred to in WO-94/14478) may be used.

The compounds of the invention may be used as X-ray contrast agents and to this end they may be formulated with conventional carriers and excipients to produce diagnostic contrast media.

Thus viewed from a further aspect the invention provides a diagnostic composition comprising a compound of formula I (as defined above) together with at least one physiologically tolerable carrier or excipient, e.g. in aqueous solution in water for injections optionally together with added plasma ions or dissolved oxygen.

The contrast agent compositions of the invention may be at ready-to-use concentrations or may be formulated in concentrate form for dilution prior to administration. Generally compositions in ready-to-use form will have iodine concentrations of at least 100mgI/ml, preferably at least 150 mgI/ml, with concentrations of at least 300mgI/ml, e.g. 320 to 400 mgI/ml being generally preferred. The higher the iodine concentration the higher the diagnostic value but equally the higher the solution's viscosity and osmolality. Normally the maximum iodine concentration for a given compound will be determined by its solubility, and by the upper tolerable limits for viscosity and osmolality.

For contrast media which are administered by injection, the desirable upper limit for solution viscosity at ambient temperature (20°C) is 30mPas; however viscosities of up to 50 or even up to 60mPas can be tolerated although their use in paediatric radiography will then generally be contraindicated. For contrast media which are to be given by bolus injection, e.g. in angiographic procedures, osmotoxic effects must

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be considered and preferably osmolality should be below 1 Osm/kg H<sub>2</sub>O, especially below 850 mOsm/kg H<sub>2</sub>O, in particular within 50 or less, preferably within 10, mOsm of isotonicity (about 300 mOsm/kg H<sub>2</sub>O).

5           With the compounds of the invention, such viscosity, osmolality and iodine concentration targets can readily be met. Indeed effective iodine concentrations may be reached with hypotonic solutions. It may thus be desirable to make up solution tonicity by  
10           the addition of plasma cations so as to reduce the toxicity contribution which derives from ionic imbalance effects following bolus injection. Such cations will desirably be included in the ranges suggested in WO-90/01194 and WO-91/13636.

15           Preferred plasma cation contents for the contrast media of the invention, especially contrast media for angiography, are as follows:

20	sodium	2 to 100, especially 15 to 75, particularly 20 to 70, more particularly 25 to 35 mM
25	calcium	up to 3.0, preferably 0.05 to 1.6, especially 0.1 to 1.2, particularly 0.15 to 0.7mM
	potassium	up to 2, preferably 0.2 to 1.5, especially 0.3 to 1.2, particularly 0.4 to 0.9 mM
30	magnesium	up to 0.8, preferably 0.05 to 0.6, especially 0.1 to 0.5, particularly 0.1 to 0.25 mM

35           The plasma cations may be presented, in whole or in part, as counterions in ionic contrast agents. Otherwise they will generally be provided in the form of salts with physiologically tolerable counteranions, e.g.



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chloride, sulphate, phosphate, hydrogen carbonate, etc., with plasma anions especially preferably being used.

Besides plasma cations, the contrast media may contain other counterions where the dimer is ionic and such counterions will of course preferably be physiologically tolerable. Examples of such ions include alkali and alkaline earth metal ions, ammonium, meglumine, ethanolamine, diethanolamine, chloride, phosphate, and hydrogen carbonate. Other counterions conventional in pharmaceutical formulation may also be used. The compositions moreover may contain further components conventional in X-ray contrast media, e.g. buffers, etc.

Publications referred to herein are incorporated herein by reference.

The invention will now be described further with reference to the following non-limiting Examples.

Example 1: 1,3,5-Triiodo-2,4-di(1,2,3-trihydroxy-1-propyl)-6-(3-hydroxy-1-propen-1-yl)benzene.

a. 1,3,5-Triiodo-2,4,6-trimethylbenzene

Iodine (19.0 g, 75 mmol) was dissolved in carbon tetrachloride (75 ml). Mesitylene (7.0 ml, 50 mmol) and bis(trifluoroacetoxy)phenyl iodide (35.5 g, 82 mmol) were added and the solution was stirred at ambient temperature for 2 hours. The precipitate, which was collected by filtration, was washed with cold carbon tetrachloride and dried. Yield: 20.5 g (82 %).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 3.31 (s).

b. 1,3,5-Triiodo-2,4,6-triacetoxymethylbenzene

Triiodomesitylene (19.5 g, 39 mmol) was added to glacial acetic acid (200 ml) containing acetic anhydride (400 ml) and concentrated sulfuric acid (40 ml). Solid

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potassium permanganate (24.6 g, 156 mmol) was then added in small portions over a period of 3 h. After stirring for 16 h, the solvent was evaporated and water (200 ml) was added. The aqueous suspension was extracted with  
5 dichloromethane (250 ml) and the organic phase was washed with water (3x50 ml), dried ( $\text{MgSO}_4$ ) and evaporated. The solid residue was suspended in acetone and the white crystalline product was collected by filtration. Yield: 9.3 g (35 %).  
10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 5.66 (s, 6H), 2.20 (s, 9H).

c. 1,3,5-Triiodo-2,4,6-trihydroxymethylbenzene

1,3,5-Triiodo-2,4,6-triacetoxymethylbenzene (9.3 g, 13.8  
15 mmol) was suspended in methanol (120 ml) and  $\text{K}_2\text{CO}_3$  (0.32 g, 2.3 mmol) was added. The mixture was stirred at ambient temperature for 16 h, and , after neutralization of the solution with 2M aqueous HCl, the organic solvent was evaporated. The residue was suspended in  
20 water and the white solid was collected by filtration and washed with water, methanol and ether. Yield: 7.1 g (94 %).  
 $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 5.08 (s, 6H), 3.35 (br s, 3H).

25 d. 1,3,5-Triiodobenzene-2,4,6-trialdehyde

1,3,5-Triiodo-2,4,6-trihydroxymethylbenzene (4.5 g, 8.2  
mmol) was dissolved in DMSO (80 ml). Triethylamine (51.7  
ml, 371 mmol) and pyridine- $\text{SO}_3$  (11.8 g, 74.2 mmol) were  
30 added and the mixture was stirred for two hours. The two phases were separated and the lower phase was cooled to 0 °C, poured into water (150 ml) and stirred for 30 min at 0 °C. The white solid was collected by filtration, washed with water and dried. Yield: 3.0 g  
35 (67 %).  
 $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 9.64 (s).

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e. 1,3,5-Triiodo-2,4,6-tris(2-prop-1-enoic acid)benzene methyl ester

Sodium hydride (194 mg 80 % in mineral oil, 6.5 mmol) was dissolved in DMSO (13 ml) and triethylphosphonoacetate (1.16 ml, 5.80 mmol) was added. After stirring the solution for 30 min, 1,3,5-triiodobenzene-2,4,6-trialdehyde (700 mg, 1.30 mmol) was added and the reaction mixture was stirred for 16 h. Water (200 ml) was then added and the pH was adjusted to 1 with 2 M aqueous HCl. The slurry was extracted with dichloromethane (2x200 ml) and the combined organic phases were washed with water (3x50 ml), dried (MgSO<sub>4</sub>) and evaporated. Purification by column chromatography (silica gel CH<sub>2</sub>Cl<sub>2</sub>-methanol 99:1) gave the pure product as a white solid. Yield: 426 mg (44 %).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.48 (d, 3H, J 16.2 Hz), 5.95 (d, 3H, J 16.2 Hz), 4.30 (q, 6H, J 7.2 Hz), 1.36 (t, 9H, J 7.2 Hz).

f. 1,3,5-Triiodo-2,4,6-tris(1-hydroxyprop-en-3-yl)benzene

1,3,5-Triiodo-2,4,6-tris(2-prop-1-enoic acid)benzene methyl ester (650 mg, 0.87 mmol) was dissolved in toluene (10 ml) and diisobutylaluminium hydride (5.44 ml of a 1.2 M solution in toluene) was added at 0 °C. After stirring for 40 min at 0 °C, the solution was poured into methanol (50 ml) and the resulting slurry was stirred for another 45 min. The solids were filtered off and the solution was evaporated giving a white solid residue which was purified by trituration with diethyl ether. Yield: 510 mg (94 %).  
<sup>1</sup>H NMR (CD<sub>3</sub>OD): 6.44 (d, 3H, J 16.0 Hz), 5.57 (dt, 3H, J<sub>d</sub> 16.0 Hz, J<sub>t</sub> 5.8 Hz), 4.23 (m, 6H).

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g. 1,3,5-Triiodo-2,4,6-tris(1-acetoxyprop-en-3-yl)benzene

1,3,5-Triiodo-2,4,6-tris(1-hydroxyprop-en-3-yl)benzene  
5 (560 mg, 0.90 mmol) was dissolved in a mixture of pyridine (8 ml) and acetic anhydride (8 ml). After stirring at ambient temperature for 16 hours, the solvent was evaporated and the residue was purified by preparative HPLC (RP-18, CH<sub>3</sub>CN: H<sub>2</sub>O 80:20). Yield 310 mg  
10 (46 %).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.46 (dt, 3H, J<sub>d</sub> 16.2 Hz, J<sub>t</sub> 1.6 Hz), 5.68 (dt, 3H, J<sub>d</sub> 16.2 Hz, J<sub>t</sub> 5.6 Hz), 4.83 (dd, 6H, J<sub>1</sub> 5.6 Hz, J<sub>2</sub> 1.6 Hz), 2.12 (s, 9H).  
<sup>13</sup>CNMR (CDCl<sub>3</sub>): 170.6, 146.3, 140.9, 131.5, 98.7, 63.5,  
15 20.9.

h. 1,3,5-Triiodo-2,4-di(1,2,3-trihydroxy-1-propyl)-6-(3-hydroxy-1-propen-1-yl)benzene

1,3,5-Triiodo-2,4,6-tris(1-acetoxyprop-en-3-yl)benzene  
20 (100 mg, 0.133 mmol) was dissolved in formic acid (5 ml) containing hydrogen peroxide (0.054 ml). The mixture was stirred at ambient temperature for 21 hours and the solvent was evaporated. Methanol (5 ml) was added  
25 followed by solid K<sub>2</sub>CO<sub>3</sub> (195 mg), and, after stirring for 1 hour, the solvent was evaporated. The product was purified by preparative HPLC (CH<sub>3</sub>CN: H<sub>2</sub>O 3:97).  
<sup>1</sup>H NMR (D<sub>2</sub>O): 6.45 (d, 1H, J 16.0 Hz), 5.40-5.55 (m, 1H), 4.54-4.90 (m, 11H), 4.23-4.31 (m, 2H), 3.62- 3.91 (m,  
30 4H).  
MS (ESP): 692 (M<sup>+</sup>).

Example 2: 1,3,5-Triiodo-2,4,6-tri(1,2,3-trihydroxy-1-propyl)benzene.

35 1,3,5-Triiodo-2,4,6-tris(1-acetoxyprop-en-3-yl)benzene (100 mg, 0.133 mmol, from Example 1g) was dissolved in

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formic acid (5 ml) containing hydrogen peroxide (0.081 ml). The mixture was stirred at room temperature for 40 hours and the solvent was evaporated. Methanol (5 ml) was added followed by solid  $K_2CO_3$  (195 mg), and, after stirring for 1 h, the solvent was evaporated. The product was purified by preparative HPLC ( $CH_3CN:H_2O$  3:97).

$^1H$  NMR ( $CD_3OD$ ): 4.57-4.94 (m, 15 H), 3.62-3.99 (m, 6H).  
MS (ESP): 744 (M+18).

Example 3: N-Acetyl-3-hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-N-(2,3-dihydroxypropyl)-2,4,6-triiodoaniline

a. 1-Hydroxymethyl-3-nitro-5-benzoic acid methyl ester

1-Nitroisophthalic acid monomethyl ester (22.5 g, 100 mmol) was dissolved in dry THF (675 ml) and  $BF_3 \cdot Et_2O$  (25.2 ml, 200 mmol) was added.  $NaBH_4$  (5.1 g, 135 mmol) was then added portionwise during 1 h. After stirring for 2 additional h, ethanol (20 ml) was added slowly followed by water (200 ml) and diethyl ether (400 ml). The phases were separated and the aqueous phase was extracted once with diethyl ether (100 ml). The combined organic phases were washed with a saturated aqueous solution of  $NaHCO_3$ , dried ( $Na_2SO_4$ ) and evaporated. Yield: 20 g (96 %). HPLC analysis indicated >95 % purity of the product.

$^1H$  NMR ( $CDCl_3$ ): 8.72 (s, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 4.86 (s, 2H), 3.97 (s, 3H), 2.37 (br s, 1H).

b. 1-Hydroxymethyl-3-nitro-5-(2,3-dihydroxypropylaminocarbonyl)benzene

The methyl ester from Example 3a (20.5 g, 97 mmol) was mixed with 2,3-dihydroxypropylamine (9.6 g, 106 mmol) and the mixture was heated to 90 °C. After 45 min, the

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pressure was reduced to 200 mm Hg and heating was continued for 2 h. The crude product, which was >95 % pure according to HPLC analysis, was used without further purification in the next step. Yield: 22.8 g (87 %).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): 8.57 (s, 1H), 8.38 (s, 1H), 8.19 (s, 1H), 4.77 (s, 2H), 3.81-3.88 (m, 1H), 3.39-3.63 (m, 4H).

10 c. 3-Hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)aniline

1-Hydroxymethyl-3-nitro-5-(2,3-dihydroxypropylaminocarbonyl)benzene (12.0 g, 44.4 mmol) was hydrogenated in methanol (150 ml) at 60 psi H<sub>2</sub> using Pd/C (10 %, 100 mg) as the catalyst. The catalyst was removed by filtration and the residue was evaporated. Addition of methanol (10 ml) precipitated the product as a white solid which was filtered off and dried. Yield: 6.6 g (62 %).

20 <sup>1</sup>H NMR (CD<sub>3</sub>OD): 7.05-7.09 (m, 1H), 6.98-7.03 (m, 1H), 6.83-6.87 (m, 1H), 4.53 (s, 2H), 3.77-3.85 (m, 1H), 3.8-3.59 (m, 4H), 3.32-3.42 (m, 1H)  
MS (ESP, m/e): 241 ([M+1]<sup>+</sup>, 100 %).

25 d. 3-Hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodoaniline

3-Hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)aniline (500 mg, 2.1 mmol) was dissolved in water (175 ml) and an aqueous solution of KICl<sub>2</sub> (70 %, w/w) was added in portions of 0.1 ml during 8 h. A total amount of 1.0 ml KICl<sub>2</sub> solution was added. After a total reaction time of 6 h, the solution was extracted with ethyl acetate (1000 ml) which was separated and washed with an aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (0.2M, 100 ml). Evaporation followed by purification by preparative HPLC gave 432 mg (33 %) of the pure product.

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<sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.10 (s, 2H), 3.90-3.98 (m, 1H), 3.72 (ddd, J<sub>1</sub>=0.7 Hz, J<sub>2</sub>=4.2 Hz, J<sub>3</sub>=11.4 Hz), 1H), 3.60 (dd, J<sub>1</sub>=6.0 Hz, J<sub>2</sub>=11.4 Hz, 1H), 3.49 (ddd, J<sub>1</sub>=1.2 Hz, J<sub>2</sub>=6.0 Hz, J<sub>3</sub>=13.5 Hz, 1H), 3.37 (ddd, J<sub>1</sub>=1.2 Hz, J<sub>2</sub>=6.1 Hz, J<sub>3</sub>=13.2 Hz, 1H), 2.62 (s, 1H), 2.28 and 2.34 (2s, 2H).  
MS (ESP, m/e): 618 (M<sup>+</sup>, 100 %), 640 ([M+Na]<sup>+</sup>, 55 %).

e. N-acetyl-3-acetoxymethyl-5-(2,3-diacetoxypropylaminocarbonyl)-2,4,6-triiodoaniline

3-Hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodoaniline (3.3 g, 5.3 mmol) was suspended in glacial acetic acid (12 ml) containing acetic anhydride (48 ml) and concentrated sulfuric acid (0.08 ml). The mixture was stirred at 60 °C for 3 h, allowed to cool to room temperature, and CH<sub>2</sub>Cl<sub>2</sub> (100 ml) and water (100 ml) were added. The organic phase was washed with water (3x50 ml) and a saturated aqueous solution of NaHCO<sub>3</sub> (2x50 ml). After drying (MgSO<sub>4</sub>) and evaporation, the residue was dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and methanol (9:1) and filtered through a short silica pad and evaporated. Yield: 3.0 g (71 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.27-8.32 (m, 1H), 5.51 (s, 2H), 5.18-5.22 (m, 1H), 4.17-4.42 (m, 2H), 3.67-3.84 (m, 1H), 3.41-3.60 (m, 1H), 2.56 (s, 3H), 2.04-2.14 (8s, 12H).  
MS (ESP, m/e): 786 (M<sup>+</sup>, 100 %), 809 ([M+Na]<sup>+</sup>, 81 %).

f. N-Acetyl-3-hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-N-(2,3-dihydroxypropyl)-2,4,6-triiodoaniline

N-acetyl-3-acetoxymethyl-5-(2,3-diacetoxypropylaminocarbonyl)-2,4,6-triiodoaniline (1.0 g, 1.27 mmol) was suspended in a mixture of methanol (6 ml) and water (30 ml) and pH was adjusted to 12.0 using a 2 M aqueous solution of NaOH. After stirring for 1 h, 1-bromo-2,3-propanediol (0.99 g, 6.4 mmol) was added and

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the pH was adjusted to 11.6 using a 2 M aqueous solution of HCl. 1-Bromo-2,3-propanediol (0.99 g, 6.4 mmol) was again added after 16 and 18 h and after 24 h, pH was adjusted to 6.5 using a 2 M aqueous solution of HCl.

5 After evaporation, the residue was purified by preparative HPLC. Yield: 0.373 g (40 %).

$^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 5.20 (s, 2H), 3.23-3.99 (m, 12H), 1.79 (2s, 3H).

MS (ESP, m/e): 734 ( $\text{M}^+$ , 60 %), 756 ( $[\text{M}+\text{Na}]^+$ , 100 %).

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Example 4. N,N'-bis(hydroxyacetyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

a. 3,5-Diaminobenzylalcohol

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A solution of 3,5-dinitrobenzylalcohol (2.20 g, 11.1 mmol) in methanol (90 ml) and a Pd/C catalyst (10 %, 100 mg) was hydrogenated in a Parr apparatus at 60 psi. The solution was filtered and the solvent was removed by evaporation. The crude product was used without purification in the next step.

20

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 6.12-6.14 (m, 2H), 5.96-5.98 (m, 1H), 4.51 (s, 2H), 3.60 (br s, 4H).

25

b. 3,5-Diamino-2,4,6-triiodobenzylalcohol

The crude product from the previous example dissolved in a mixture of methanol (310 ml) and water (60 ml) and pH was adjusted to 1.5 using a 4 M aqueous solution of HCl.

30

A solution of  $\text{KICl}_2$  (70 %, 11.2 g) was added dropwise at such a rate, that the color disappeared between each addition. After stirring for 5 additional min, the precipitate was filtered off and washed with water (3x50 ml), ether (3x50 ml) and dried. Yield: 4.50 g (80 %).

35

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 5.20 (s, 4H), 4.81-4.94 (m, 3H).



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c. 3,5-Diamino-2,4,6-triiodobenzylacetate

5 3,5-Diamino-2,4,6-triiodobenzylalcohol (4.42 g, 8.56 mmol) was dissolved in a mixture of pyridine (50 ml) and acetic anhydride (2.5 ml) and the mixture was stirred at room temperature for 16 h. The solvents were evaporated and the residue was washed with ether (3x50 ml), water (3x50 ml) and dried. Yield: 4.52 g (95 %).

10  $^1\text{H}$  NMR (DMSO- $d_6$ ): 5.35 (s, 2H), 5.28 (s, 4H), 2.04 (s, 3H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 170.5, 148.1, 139.0, 78.0, 73.6, 70.0, 20.8.

15 d. 3,5-Bis(acetoxycetyl-amino)-2,4,6-triiodobenzylacetate

3,5-Diamino-2,4,6-triiodobenzylacetate (5.58 g, 10 mmol) was mixed with acetoxycetyl chloride (3.22 ml, 30 mmol) and dimethylacetamide (50 ml) and the mixture was stirred for 17 h. Ether (600 ml) was added, and after 20 min, the precipitate was collected, washed with water (3x50 ml) and dried. Recrystallization from acetonitrile gave 3.3 g (44 %) of the pure product.

25  $^1\text{H}$  NMR (DMSO- $d_6$ ): 10.27 and 10.19 (2s, 2:1, 2H), 5.51 (s, 2H), 4.66 (s, 4H), 2.13 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H).

30 e. N,N'-bis(hydroxyacetyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

3,5-Bis(acetoxycetyl-amino)-2,4,6-triiodobenzylacetate (152 mg, 0.2 mmol) was dissolved in a mixture of methanol (6 ml) and 1 M aqueous NaOH (2 ml) and the solution was stirred for 2 h at room temperature. After neutralization with 1 M HCl, the solvents were removed by evaporation and the product was purified by preparative HPLC. Yield: 105 mg (83 %).

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MS (ESP, m/e): 655 ( $[M+Na]^+$ , 100 %).

Example 5. N,N'-Bis(hydroxyacetyl)-N-(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

5

a. N,N'-Bis(acetoxyacetyl)-N-(2-acetoxyethyl)-3,5-diamino-2,4,6-triiodobenzylacetate

3,5-Bis(acetoxyacetyl-amino)-2,4,6-triiodobenzylacetate  
10 (2.15 g, 2.84 mmol) was dissolved in a mixture of DMSO (5 ml) and dimethylacetamide (5 ml) containing  $Cs_2CO_3$  (1.0 g, 3.07 mmol) and 2-bromoethyl acetate (0.31 ml, 2.84 ml). The mixture was stirred at room temperature for 48 h, ether (100 ml) and aqueous  $NaH_2PO_4$  buffer were  
15 added and the organic phase was washed with water and dried. Purification by preparative HPLC gave 520 mg (22 %) of the product.

$^1H$  NMR ( $CDCl_3$ ): 7.86 (s, 1H), 5.66 (s, 2H), 4.80 (s, 2H), 3.81-4.44 (m, 6H), 2.13-2.27 (m, 12H).

20 MS (ESP, m/e): 845 ( $[M+1]^+$ , 100 %), 866 ( $[M+Na]^+$ , 24 %).

b. N,N'-Bis(hydroxyacetyl)-N-(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

25 N,N'-Bis(acetoxyacetyl)-N-(2-acetoxyethyl)-3,5-diamino-2,4,6-triiodobenzylacetate (0.50 g, 0.59 mmol) was dissolved in a mixture of methanol (5 ml), water (5 ml) and aqueous 1 M NaOH (1 ml). The solution was stirred for 2 h, pH was adjusted to 2 using aqueous HCl and the  
30 product was purified by preparative HPLC. Yield: 240 mg (67 %).

$^1H$  NMR  $DMSO-d_6$ : 9.85 (br s, 1H), 5.77 (br s, 1H), 4.79-5.26 (m, 3H), 3.20-3.71 (m, 6H).

MS (ESP, m/e): 676 ( $M^+$ , 57 %), 698 ( $[M+Na]^+$ , 100 %).

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Example 6. N,N'-Bis(hydroxyacetyl)-N,N'-bis(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

3,5-Bis(acetoxyacetyl-amino)-2,4,6-triiodobenzylacetate  
5 (190 mg, 0.25 mmol), prepared according to Example 4,  
was dissolved in dimethylacetamide (5 ml) under an argon  
atmosphere. 2-Bromoethyl acetate (0.22 ml, 2.0 mmol) and  
K<sub>2</sub>CO<sub>3</sub> (138 mg, 1.0 mmol) were added. After 16 h, DMSO  
(1.5 ml), 2-bromoethyl acetate (0.22 ml, 2.0 mmol) and  
10 K<sub>2</sub>CO<sub>3</sub> (138 mg, 1.0 mmol) were added and the suspension  
was stirred for another 24 h. Aqueous NaH<sub>2</sub>PO<sub>4</sub> was added  
and the resulting solution was extracted with ether  
(3x25 ml). The combined organic phases were washed with  
water (4x20 ml) and then dried (MgSO<sub>4</sub>). The solvent was  
15 removed by evaporation and the residue, a colorless oil,  
was dissolved in a mixture of methanol (3 ml) and 1 M  
aqueous NaOH (3 ml). The solution was stirred for 1 h,  
pH was adjusted to 6 using aqueous HCl and the solvents  
were removed by evaporation. Purification by preparative  
20 HPLC gave 60 mg (33 %) of the product.  
MS (ESP, m/e): 720 (M<sup>+</sup>, 100 %), 742 ([M+Na]<sup>+</sup>, 36 %).

Example 7. N,N'-Bis(hydroxyacetyl)-N-(2,3-dihydroxypropyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

25 a. N,N'-Bis(acetoxyacetyl)-N-[(2,2-dimethyl-1,3-dioxolane-4-yl)-methyl]-3,5-diamino-2,4,6-triiodobenzylacetate

30 3,5-Bis(acetoxyacetyl-amino)-2,4,6-triiodobenzylacetate  
(90 mg, 0.12 mmol), prepared according to Example 4, was  
dissolved in a mixture of dimethylacetamide (3 ml) and  
DMSO (3 ml). 4-Bromomethyl-2,2-dimethyl-1,3-dioxolane  
(0.097 g, 0.5 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (0.10 g, 0.3 mmol) were  
35 added and the solution was stirred at room temperature  
for 48 h. Aqueous NaH<sub>2</sub>PO<sub>4</sub> was added and the solution was  
extracted with ether (3x25 ml). The combined organic

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phases were washed with water (3x15 ml), dried (MgSO<sub>4</sub>) and evaporated. Purification by preparative HPLC gave 36 mg (35 %) of the pure product.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 10.30 (br s, 1H), 5.53 (s, 2H), 3.61-4.68 (m, 9H), 2.13 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.17-1.34 (m, 6H).  
MS (ESP, m/e): 894 ([M+Na]<sup>+</sup>, 100 %), 910 ([M+K]<sup>+</sup>, 11 %).

10 b. N,N'-Bis(hydroxyacetyl)-N-(2,3-dihydroxypropyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

N,N'-Bis(acetoxyacetyl)-N-[(2,2-dimethyl-1,3-dioxolane-4-yl)-methyl]-3,5-diamino-2,4,6-triiodobenzylacetate (36 mg, 0.042 mmol) was dissolved in a mixture of methanol (3 ml) and water (4 ml) and the pH was adjusted to 12 using a 1 M aqueous solution of NaOH. After stirring for 2 h, pH was adjusted to 1 using 1 M aqueous HCl and stirring was continued for 16 h. The solution was neutralized with an aqueous NaH<sub>2</sub>PO<sub>4</sub> buffer, the solvents were removed by evaporation and the residue was purified by preparative HPLC to give 24 mg (81 %) of the pure product.

MS (ESP, m/e): 704 (M<sup>+</sup>, 100 %), 726 ([M+Na]<sup>+</sup>, 34 %).

25 Example 8. N,N'-Bis(2-hydroxypropionyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

a. N,N'-Bis(2-acetoxypropionyl)-3,5-diamino-2,4,6-triiodobenzylacetate

30 3,5-Diamino-2,4,6-triiodobenzylacetate (2.79 g, 5.0 mmol) was dissolved in dimethylacetamide (25 ml) and cooled to 0 °C. 2-Acetoxypropionyl chloride (3.73 g, 25 mmol) was added dropwise and the mixture was stirred at room temperature for 17 h. The solvents were evaporated and the residue was triturated with diethyl ether. The solid residue was then purified by flash chromatography

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on silica gel using a mixture of  $\text{CH}_2\text{Cl}_2$  and acetonitrile (5:1) as the eluent. Yield: 2.21 g (56 %).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 10.20-10.23 (m, 2H), 5.52 (s, 2H), 5.21-5.24 (m, 2H), 2.06-2.13 (m, 9H), 1.51 (d,  $J=6.9$  Hz, 6H).

b. N,N'-Bis(2-hydroxypropionyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

10 N,N'-Bis(2-acetoxypionyl)-3,5-diamino-2,4,6-triiodobenzylacetate (0.16 g, 0.2 mmol) was dissolved in a mixture of methanol (5 ml) and water (5 ml) and the pH was adjusted to 12 using a 1 M aqueous solution of NaOH. After stirring for 15 h, the solution was  
15 neutralized with 1 M HCl and the solvents were removed by evaporation. Purification by preparative HPLC gave 61 mg (46 %) of the pure product.  
MS (ESP, m/e): 660 ( $\text{M}^+$ , 5 %), 682 ( $[\text{M}+\text{Na}]^+$ , 100 %), 698 ( $[\text{M}+\text{K}]^+$ , 17 %).

20 Example 9. N,N'-Bis(2-hydroxypropionyl)-N-(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

25 a. N,N'-Bis(2-acetoxypionyl)-N-(2-acetoxyethyl)-3,5-diamino-2,4,6-triiodobenzylacetate

N,N'-Bis(2-acetoxypionyl)-3,5-diamino-2,4,6-triiodobenzylacetate (393 mg, 0.50 mmol) was dissolved in a mixture of dimethylacetamide (4 ml) and DMSO (4 ml)  
30 containing 2-bromoethyl acetate (0.083 g, 0.50 mmol) and  $\text{Cs}_2\text{CO}_3$  (244 mg, 0.75 mmol). The mixture was stirred for 17 h, water (20 ml) was added and the mixture was extracted with ether (3x25 ml). The combined organic phases were washed with water (3x20 ml), dried ( $\text{MgSO}_4$ )  
35 and evaporated. The residue was purified by preparative HPLC to give 80 mg (18 %) of pure product.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ): 5.72-5.82 (m, 2H), 5.20-5.42 (m, 2H),

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3.55-4.48 (m, 4H), 1.90-2.24 (m, 12H), 1.66 (d, J=7.1 Hz, 6H).

MS (ESP, m/e): 1004 ([M+Cs]<sup>+</sup>, 100 %).

5 b. N,N'-Bis(2-hydroxypropionyl)-N-(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

N,N'-Bis(2-acetoxypropionyl)-N-(2-acetoxyethyl)-3,5-diamino-2,4,6-triiodobenzylacetate (120 mg, 0.14 mmol)  
10 was dissolved in a mixture of water (7 ml) and methanol (7 ml) and pH was adjusted to 12 using an 1 M aqueous solution of NaOH. The mixture was stirred for 2 h, pH was adjusted to 7 with aqueous HCl and the solvents were evaporated. The product was purified by preparative  
15 HPLC. Yield: 70 mg (72 %).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.27-5.34 (m, 2H), 4.31-4.41 (m, 1H), 3.82-4.12 (m, 4H), 3.55-3.73 (m, 1H), 1.51-1.60 (m, 3H), 1.23-1.32 (m, 3H).

MS (ESP, m/e): 726 ([M+Na]<sup>+</sup>, 100 %).

20

Example 10. N,N'-Bis(2-hydroxypropionyl)-N,N'-bis(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

25 a. N,N'-Bis(2-acetoxypropionyl)-N,N'-bis(2-acetoxyethyl)-3,5-diamino-2,4,6-triiodobenzylacetate

N,N'-Bis(2-acetoxypropionyl)-3,5-diamino-2,4,6-triiodobenzylacetate (197 mg, 0.25 mmol) was dissolved in a mixture of dimethylacetamide (5 ml) and DMSO (1.5  
30 ml) containing 2-bromoethyl acetate (0.11 ml, 1.0 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (162 mg, 0.50 mmol). The mixture was stirred for 67 h, water (20 ml) was added and the mixture was extracted with ether (2x75 ml). The combined organic phases were washed with water (5x75 ml), dried (Na<sub>2</sub>SO<sub>4</sub>)  
35 and evaporated. The residue was purified by preparative HPLC to give 35 mg (15 %) of pure product.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 5.49-5.73 (m, 2H), 4.97-5.22 (m, 2H),

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3.49-4.00 (m, 6H), 1.86-12.08 (m, 15H), 1.09-1.58 (m, 6H).

5 b. N,N'-Bis(2-hydroxypropionyl)-N,N'-bis(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

N,N'-Bis(2-acetoxypropionyl)-N,N'-bis(2-acetoxyethyl)-3,5-diamino-2,4,6-triiodobenzylacetate (175 mg, 0.18 mmol) was dissolved in a mixture of methanol (8 ml) and water (8 ml) and pH was adjusted to 12 with 1 M aqueous NaOH. After stirring for 3 h, the solution was neutralized with aqueous HCl. Purification by preparative HPLC gave 50 mg (37 %) of the pure product.  
10 <sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.26-5.38 (m, 2H), 3.44-4.08 (m, 6H), 1.32-1.59 (m, 6H).  
15 MS (ESP, m/e): 770 ([M+Na]<sup>+</sup>, 100 %).

Example 11. N,N'-Bis(2-hydroxypropionyl)-N-(2,3-dihydroxypropyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

20

a. N,N'-Bis(acetoxypropionyl)-N-[(2,2-dimethyl-1,3-dioxolane-4-yl)-methyl]-3,5-diamino-2,4,6-triiodobenzylacetate

25 N,N'-Bis(2-acetoxypropionyl)-3,5-diamino-2,4,6-triiodobenzylacetate (393 mg, 0.50 mmol) was dissolved in a mixture of DMSO (4 ml) and dimethylacetamide (4 ml) containing Cs<sub>2</sub>CO<sub>3</sub> (1.80 g, 5.52 mmol) and 4-bromomethyl-2,2-dimethyl-1,3-dioxolane (1.0 ml). The mixture was stirred for 7 days and was then worked up analogous to Example 7a. Purification by preparative HPLC gave 115 mg (26 %) of the pure product.  
30 <sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.61-5.5.75 (m, 2H), 5.03-5.44 (m, 2H), 3.47-4.55 (m, 6H), 1.98-2.23 (m, 9H), 1.30-1.71 (m, 12H).  
35 MS (ESP, m/e): 922 ([M+Na]<sup>+</sup>, 100 %).

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b. N,N'-Bis(2-hydroxypropionyl)-N-(2,3-dihydroxypropyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

5 N,N'-Bis(acetoxypionyl)-N-[(2,2-dimethyl-1,3-dioxolane-4-yl)-methyl]-3,5-diamino-2,4,6-triiodobenzylacetate (115 mg, 0.13 mmol) was dissolved in a mixture of methanol (8 ml) and water (8 ml) and pH was adjusted to 12 with aqueous 1 M NaOH. After 2.5 h, pH was adjusted to 1 with 2 M aqueous HCl. After  
10 stirring for 17 h, the solution was neutralized with an aqueous NaH<sub>2</sub>PO<sub>4</sub> buffer and the solvents were removed by evaporation. Purification by preparative HPLC gave 65 mg (69 %) of the pure product.  
MS (ESP, m/e): 756 ([M+Na]<sup>+</sup>, 100 %).

15

Example 12. N,N'-Bis(2,3-dihydroxypropionyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

20 a. N,N'-Bis(2,2-dimethyl-1,3-dioxolane-4-carboxyl)-3,5-diamino-2,4,6-triiodobenzylacetate

3,5-Diamino-2,4,6-triiodobenzylacetate (3.54 g, 6.3 mmol) and 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid chloride (3.13 g, 19 mmol) were dissolved in  
25 dimethylacetamide (40 ml) and the solution was stirred for 3.5 h. The solvent was removed by evaporation and the residue was treated with an aqueous solution of NaHCO<sub>3</sub>. The crystalline residue was filtered off, washed with water and dried. Purification by flash  
30 chromatography using a mixture of CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN (3:1) as the eluent gave 1.90 g (37 %) of the pure product.  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 9.93-10.02 (m, 2H), 5.30 (s, 2H), 4.58 (t, J=6.2 Hz, 1H), 4.29 (t, J=7.3 Hz, 1H), 4.10 (t, J=6.1 Hz, 1H), 2.06 (s, 3H), 1.54 (s, 3H), 1.38 (s, 3H).  
35 MS (ESP, m/e): 902 ([M+dimethylacetamide]<sup>+</sup>, 100 %).



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b. N,N'-Bis(2,3-dihydroxypropionyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

5 N,N'-Bis(2,2-dimethyl-1,3-dioxolane-4-carbonyl)-3,5-diamino-2,4,6-triiodobenzylacetate (1.25 g, 1.55 mol) was dissolved in a mixture of water (50 ml), methanol (25 ml) and concentrated HCl (0.5 ml). After stirring for 4 h, the solution was neutralized with aqueous NaH<sub>2</sub>PO<sub>4</sub> and the solvents were removed by evaporation. The  
10 residue was dissolved in water (10 ml) and the pH was adjusted to 12 with aqueous NaOH. After 30 min, the solution was again neutralized and the solvent was evaporated. The product was purified by preparative HPLC. Yield: 483 mg (45 %).

15 <sup>1</sup>H NMR (9.65-9.83 (m, 2H), 5.77 (s, 2H), 5.20 (s, 1H), 4.95-5.03 (m, 2H), 4.81 (s, 2H), 4.00-4.08 (m, 2H), 3.72-3.82 (m, 2H), 3.50-3.63 (m, 2H).  
MS (ESP, m/e): 692 (M<sup>+</sup>, 62 %), 714 ([M+Na]<sup>+</sup>, 100 %).

20 Example 13. N,N'-Bis(2,3-dihydroxypropionyl)-N-(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

N,N'-Bis(2,2-dimethyl-1,3-dioxolane-4-carbonyl)-3,5-diamino-2,4,6-triiodobenzylacetate (204 mg, 0.25 mmol)  
25 was dissolved in a mixture of dimethylacetamide (4 ml) and DMSO (2.5 ml) containing Cs<sub>2</sub>CO<sub>3</sub> (650 mg, 2.0 mmol) and 2-bromoethyl acetate (0.035 ml, 0.31 mmol). After stirring for 1 week, ether (150 ml) and a NaH<sub>2</sub>PO<sub>4</sub> buffer (100 ml) were added, the organic phase was separated and  
30 the aqueous phase was extracted with ether (150 ml). The combined organic phases were then washed with water (6x100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was dissolved in a mixture of methanol (20 ml) and water (20 ml) and pH was adjusted to 12 with aqueous NaOH.  
35 After stirring for 1 h, the pH was adjusted to 1.5 with concentrated HCl and stirred for another 16 h. The solution was neutralized with aqueous NaH<sub>2</sub>PO<sub>4</sub> and the

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solvents were evaporated. Preparative HPLC gave 55 mg (30 %) of the pure product.

MS (ESP, m/e): 736 ( $M^+$ , 28 %), 758 ( $[M+Na]^+$ , 100 %).

5 Example 14. N,N'-Bis(2,3-dihydroxypropionyl)-N,N'-bis(2-hydroxyethyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

N,N'-Bis(2,2-dimethyl-1,3-dioxolane-4-carbonyl)-3,5-diamino-2,4,6-triiodobenzylacetate (204 mg, 0.25 mmol)  
10 was dissolved in a mixture of dimethylacetamide (5 ml) and DMSO (1.5 ml) containing  $K_2CO_3$  (276 mg, 2.0 mmol) and 2-bromoethyl acetate (0.44 ml, 4.0 mmol). After stirring for 48 h, an aqueous  $NaH_2PO_4$  buffer was added and the mixture was extracted with ether (2x150 ml). The  
15 combined organic phases were washed with water (6x100 ml), dried ( $Na_2SO_4$ ) and evaporated. The solid residue was dissolved in a mixture of methanol (12 ml) and water (12 ml) and the pH was adjusted to 12 with aqueous NaOH. After stirring for 18 h, the solution was acidified with  
20 concentrated HCl (0.70 ml) and stirring was continued for 3 h. The solution was neutralized and the solvents were removed by evaporation. The product was purified by preparative HPLC. Yield: 98 mg (50 %).  
MS (ESP, m/e): 802 ( $[M+Na]^+$  100 %).

25

Example 15. N,N'-Bis(2,3-dihydroxypropionyl)-N-(2,3-dihydroxypropyl)-3,5-diamino-2,4,6-triiodobenzylalcohol

N,N'-Bis(2,2-dimethyl-1,3-dioxolane-4-carbonyl)-3,5-diamino-2,4,6-triiodobenzylacetate (408 mg, 0.50 mmol)  
30 was dissolved in a mixture of dimethylacetamide (4 ml) and DMSO (4 ml) containing  $Cs_2CO_3$  (1.80 g, 5.52 mmol) and 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid chloride (2.0 ml). After stirring for 8 days, aqueous  $NaH_2PO_4$  (100  
35 ml) was added and the mixture was extracted with diethyl ether (2x150 ml). The combined organic phases were washed with water (6x100 ml), dried ( $Na_2SO_4$ ) and

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evaporated. The residue was dissolved in a mixture of methanol (10 ml) and water (10 ml) and pH was adjusted to 12 with aqueous NaOH. After stirring for 2 h, concentrated HCl (1.0 ml) was added and stirring was continued for 16 h. After neutralization, the solvents were evaporated and the residue was purified by preparative HPLC. Yield: 149 mg (39 %). MS (ESP, m/e): 766 ( $M^+$ , 60 %), 788 ( $[M+Na]^+$ , 100 %).

10 Example 16. Oxalic bis[3-hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodobenzeneamide]

a. 3-Acetoxymethyl-5-(2,3-diacetoxypropylaminocarbonyl)-2,4,6-triiodoaniline

15 3-Hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodoaniline (1.89 g, 3.06 mmol) prepared according to Example 3d, was dissolved in a mixture of acetic anhydride (5 ml) and pyridine (5 ml). The mixture was stirred at room temperature for 24 h,  $CH_2Cl_2$  (100 ml) was added and the solution was washed with water (3x25 ml), with a saturated aqueous solution of  $NaHCO_3$ , dried ( $Na_2SO_4$ ) and evaporated. The product was purified by flash chromatography on silica gel using a mixture of  $CH_2Cl_2$  and methanol (98:2) as the eluent. Yield: 1.30 g (57 %).

$^1H$  NMR ( $CDCl_3$ ): 6.10-6.25 (m, 1H), 5.48 (s, 2H), 5.20-5.28 (m, 1H), 4.22-4.43 (m, 2H), 3.53-3.89 (m, 2H), 2.06-2.13 (m, 9H).

30 MS (ESP, m/e): 744 ( $M^+$ , 100 %).

b. Oxalic bis[3-hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodobenzeneamide]

35 3-Acetoxymethyl-5-(2,3-diacetoxypropylaminocarbonyl)-2,4,6-triiodoaniline (100 mg, 0.134 mmol) was dissolved in dioxane (1.0 ml) and the solution was heated to 90

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°C. Oxalyl chloride (0.096 mmol) was added and the mixture was stirred at 78 °C for 17 h. After cooling to room temperature, water (1.0 ml) was added and pH was adjusted to 12 with aqueous NaOH. After stirring for 4 h, the solution was neutralized, the solvents were evaporated and the residue was purified by preparative HPLC. Yield : 14 mg (16 %).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.24 (s, 2H), 3.38-4.03 (m, 10H).

MS (ESP. m/e): 1290 (M<sup>+</sup>, 33 %), 1312 ([M+Na]<sup>+</sup>, 100 %).

10

Example 17. Malonic bis[3-hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodobenzeneamide]

3-Acetoxymethyl-5-(2,3-diacetoxypropylaminocarbonyl)-2,4,6-triiodoaniline (100 mg, 0.134 mmol) prepared according to Example 16a, was dissolved in dioxane (1.0 ml) and malonyl chloride (0.097 mmol) was added. The mixture was stirred at 90 °C for 2 h and the solution was allowed to cool to room temperature. Water (1 ml) was added and pH was adjusted to 12 with aqueous NaOH. After stirring at 60 °C for 18 h, the solution was neutralized and the solvents were evaporated. The product was purified by preparative HPLC. Yield: 34 mg (39 %).

MS (ESP, m/e): 1304 (M<sup>+</sup>, 68 %), 1326 ([M+Na]<sup>+</sup>, 100 %).

25

Example 18. N,N'-diacetyl-N,N'-bis[3-hydroxymethyl-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-1,3-diamino-2-hydroxypropane

30

N-acetyl-3-acetoxymethyl-5-(2,3-diacetoxypropylaminocarbonyl)-2,4,6-triiodoaniline (300 mg, 0.38 mmol) prepared according to Example 3e was dissolved in a mixture of water (1.2 ml) and methanol (0.2 ml) and pH was adjusted to 12 with aqueous NaOH. Epichlorohydrine (0.28 mmol) was added and the mixture was stirred at room temperature for 65 h. The solution

35

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was neutralized and the product was isolated by preparative HPLC. Yield: 60 mg (20 %).  
MS (ESP, m/e): 1398 ( $[M+Na]^+$ , 100 %).

5     Example 19. N-[3-hydroxymethyl-5-(2,3-  
       dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-  
       N'[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-  
       triiodophenyl]urea

10    a. N-[3-acetoxymethyl-5-(2,3-  
       diacetoxypylaminocarbonyl)-2,4,6-triiodophenyl]-  
       N'[3,5-bis(2,3-diacetoxypylaminocarbonyl)-2,4,6-  
       triiodophenyl]urea

15     3,5-Bis(2,3-diacetoxypylaminocarbonyl)-2,4,6-  
       triiodoaniline (260 mg, 0.30 mmol) was dissolved in  
       dioxane (1.0 ml) and a solution of phosgene in toluene  
       (1.93 M, 1.8 ml) was added. The flask was tightly sealed  
       and then heated to 60 °C for 17 h. After cooling to room  
20     temperature, the solvent was distilled off at reduced  
       pressure. Dioxane (3 ml) was added and distilled off  
       again. This procedure was repeated twice. Dioxane (1 ml)  
       was added followed by 3-acetoxymethyl-5-(2,3-  
       diacetoxypylaminocarbonyl)-2,4,6-triiodoaniline  
25     (0.245 g, 0.31 mmol), prepared according to Example 16a,  
       and  $Hg(OCOCH_3)_2$  (20 mg). The mixture was stirred for 16 h  
       at room temperature, the solvent was evaporated and the  
       residue was purified by preparative HPLC. Yield: 0.192 g  
       (39 %).  
30     MS (ESP, m/e): 1643 ( $M^+$ , 100 %), 1665 ( $[M+Na]^+$ , 34 %).

b. N-[3-hydroxymethyl-5-(2,3-  
       dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-  
       N'[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-  
35     triiodophenyl]urea

The product from Example 19a was dissolved in a mixture

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of methanol (5 ml) and water (5 ml) and the pH was adjusted to 12 using a 2 M aqueous solution of NaOH. After stirring for 2 h, the pH was adjusted to 6.5 using aqueous HCl and the solvents were evaporated. The product was purified using preparative HPLC. Yield: 68 mg (44 %). MS (ESP, m/e): 1349 ( $M^+$ , 15 %), 1372 ( $[M+Na]^+$ , 100 %).

Example 20. N-Hydroxyacetyl-3-(1,2-dihydroxyethyl)-5-(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodoaniline

a. 3-Nitro-5-(2-trimethylsilylvinyl)benzoic acid methyl ester

A mixture of 3-iodo-5-nitrobenzoic acid methyl ester (307 mg, 1.0 mmol),  $Pd(OAc)_2$  (67 mg, 0.30 mmol), triphenylphosphine (0.032 g, 0.60 mmol),  $AgNO_3$  (170 mg, 1.0 mmol), triethylamine (0.167 ml, 1.2 mmol) and vinyltrimethylsilane (0.309 ml, 2.0 mmol) was dissolved in acetonitrile (10 ml) and the solution was heated to 60 °C in a closed vessel for 48 h. The precipitated salts were filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel using a mixture of ethyl acetate and heptane (1:11) as the eluent. Yield: 210 mg (75 %).  $^1H$  NMR ( $CDCl_3$ ): 8.70-8.73 (m, 1H), 8.36-8.47 (m, 2H), 6.93 (d,  $J=19.2$  Hz, 1H), 6.75 (d,  $J=19.2$  Hz, 1H), 3.99 (s, 3H), 0.20 (s, 9H). MS (APci, m/e): 279 ( $M^+$ , 100 %).

b. 3-Nitro-5-vinylbenzoic acid methyl ester

3-Nitro-5-(2-trimethylsilylvinyl)benzoic acid methyl ester (2.44 g, 8.71 mmol) was dissolved in acetonitrile (150 ml), the solution was heated to reflux temperature and HCl gas was bubbled through the solution until the starting material had disappeared according to HPLC

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analysis. The solution was allowed to cool and the solvent was removed by evaporation. The residue was >95 % pure according to HPLC and was used without further purification. Yield: 2.02 g (89 %).

5  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ): 8.64 (s, 1H), 8.54 (s, 1H), 8.45 (s, 1H), 6.96 (dd,  $J_1=10.8$  Hz,  $J_2=17.4$  Hz, 1H), 6.11 (d,  $J=17.4$  Hz, 1H), 5.59 (d,  $J=10.8$  Hz, 1H), 4.00 (s, 3H).

10 c. 3-Nitro-5-(1,2-dihydroxyethyl)benzoic acid methyl ester

3-Nitro-5-vinylbenzoic acid methyl ester (2.02 g, 9.76 mmol) was dissolved in a mixture of acetone and water (200 ml, 9:1), and, after cooling to 0 °C,  $\text{OsO}_4$  (60 mg, 0.24 mmol) was added followed by N-methylmorpholine-N-oxide (2.34 g, 20.0 mmol). After stirring for 46 h at room temperature, an aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_5$  (3.7 g) in water (150 ml) was added and the solution was acidified with dilute aqueous HCl. The volume of the solution was reduced to 150 ml by evaporation and the residue was extracted with ethyl acetate (3x100 ml). The combined organic phases were evaporated and the residue was purified by column chromatography on silica gel using ethyl acetate as the eluent. Yield: 1.60 g (60 %).

25  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ): 8.62-8.66 (m, 1H), 8.44-8.48 (m, 1H), 8.36-8.40 (m, 1H), 4.88-4.94 (m, 1H), 3.98 (s, 3H), 3.60-3.79 (m, 4H).

30 d. 1-(2,3-Dihydroxypropylaminocarbonyl)-3-nitro-5-(1,2-dihydroxyethyl)benzene

3-Nitro-5-(1,2-dihydroxyethyl)benzoic acid methyl ester (0.40 g, 1.69 mmol) and 2,3-dihydroxypropylamine (0.17 g, 1.86 mmol) were dissolved in methanol (2 ml) and the solution was stirred at 75 °C for 1 h. The pressure was then reduced to 200 mm Hg and stirring was continued at 95 °C for 2 h. The crude reaction mixture was purified

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by preparative HPLC. Yield: 0.40 g (78 %).

MS (ESP, m/e): 299 ( $[M-1]^+$ , 100 %).

5 e. 3-(2,3-Dihydroxypropylaminocarbonyl)-5-(1,2-dihydroxyethyl)aniline

10 1-(2,3-Dihydroxypropylaminocarbonyl)-3-nitro-5-(1,2-dihydroxyethyl)benzene (0.40 g, 1.32 mmol) was dissolved in a mixture of methanol (40 ml) and water (20 ml). The solution was hydrogenated at 60 psi using a Pd/C catalyst (10 %, 50 mg). The solution was filtered through celite and the solvents were removed by evaporation. The product was >95 % pure by HPLC analysis and was used without further purification.

15 MS (ESP, m/e): 271 ( $[M+1]^+$ , 100 %), 293 ( $[M+Na]^+$ , 45 %).

f. 3-(2,3-Dihydroxypropylaminocarbonyl)-5-(1,2-dihydroxyethyl)-2,4,6-triodoaniline

20 3-(2,3-Dihydroxypropylaminocarbonyl)-5-(1,2-dihydroxyethyl)aniline (0.37 g, 1.35 mmol) was dissolved in a mixture of methanol (30 ml) and water (90 ml).  $KICl_2$  (1.37 g, 4.05 mmol) was added and the solution was stirred at 35 °C for 24 h. Additional  $KICl_2$  (1.0 mmol) was added, and stirring was continued at 60 °C for 72 h. An aqueous solution of  $Na_2S_2O_5$  (1.0 g in 50 ml) was added and the solvents were removed by evaporation. Purification by preparative HPLC gave 87 mg (10 %) of the pure product.

30  $^1H$  NMR ( $CD_3OD$ ): 8.60 (m, 1H), 5.38-5.47 (m, 1H), 3.96-4.26 (m, 3H), 3.30-3.84 (m, 10 H).

MS (ESP, m/e): 648 ( $M^+$ , 15 %), 670 ( $[M+Na]^+$ , 100 %).

35 g. N-Hydroxyacetyl-3-(2,3-dihydroxypropylaminocarbonyl)-5-(1,2-dihydroxyethyl)-2,4,6-triodoaniline

3-(2,3-Dihydroxypropylaminocarbonyl)-5-(1,2-



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dihydroxyethyl)-2,4,6-triiodoaniline (0.059 d, 0.091 mmol) was mixed with acetoxyacetyl chloride (1.0 ml) containing N,N-dimethylacetamide (0.4 ml) and the mixture was stirred at 60 °C for 48 h. The mixture was allowed to cool to room temperature, water was added and the solvents were removed by evaporation. The residue was dissolved in a mixture of methanol (10 ml) and water (5 ml) and an aqueous solution of NaOH (5 M, 1 ml) was added. The solution was stirred at room temperature for 1 h, the solution was neutralized with aqueous HCl and the solvents were evaporated. Purification by HPLC gave the pure product.  
MS (ESP, m/e): 706 (M<sup>+</sup>, 100 %).

Example 21. 3,5-Di(hydroxyacetyl-amino)-2,4,6-triiodoacetophenone

a. 1,3-Diamino-5-(1-hydroxyethyl)benzene

3,5-Dinitroacetophenone (2.02 g, 9.5 mmol) which had been prepared according to the literature procedure (Y. Nagase et al., Macromol. Chem. Rapid Comm. (1990) 11, 185-191) was dissolved in methanol (100 ml) and hydrogenated at 60 psi using a Pd/C catalyst (5 %, 100 mg). The catalyst was filtered off and the solvent was removed by evaporation. The product was used without purification in the next step. Yield: 1.22 g (84 %).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.20 (d, J=2.0 Hz, 2H), 6.08 (t, J=2.0 Hz, 1H), 4.90 (br s, 4H), 4.62 (q, J=7.0 Hz, 1H), 3.37 (d, J=7.0 Hz, 3H).  
MS (ESP, m/e): 151 ([M-1]<sup>+</sup>, 100 %).

b. 1,3-Diamino-2,4,6-triiodoacetophenone

1,3-Diamino-5-(1-hydroxyethyl)benzene (1.18 g, 7.72 mmol) was dissolved in a mixture of methanol and water (5:1, 168 ml) containing 1 M aqueous HCl (16 ml). An

- 40 -

aqueous solution of  $\text{KICl}_2$  (7.31 g, 30.9 mmol) was added quickly, and, after stirring for 50 min, the solid was filtered off, washed with water and dried. The product was pure by TLC and  $^1\text{H}$  NMR analysis. Yield: 3.62 g (89 %).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 4.86 (br s, 4H), 2.62 (s, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 204.7, 151.1, 146.8, 28.7.

MS (APci, m/e): 528 ( $\text{M}^+$ , 100 %).

10 c. 1,3-Di(acetoxycetyl-amino)-2,4,6-triiodoacetophenone

1,3-Diamino-2,4,6-triiodoacetophenone (1.8 g, 3.41 mmol) was dissolved in dimethylacetamide (15 ml) containing acetoxycetyl chloride (1.1 ml, 10.2 mmol) and the solution was stirred for 65 h at room temperature. The solvents were removed by evaporation and the residue was purified by preparative HPLC. Yield: 1.69 g (68 %).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 10.13-10.27 (m, 2H), 4.65 (s, 4H), 2.56 (s, 3H), 2.12 (s, 6H).

20 MS (ESP, m/e): 750 ( $[\text{M}+\text{Na}]^+$ , 100 %), 766 ( $[\text{M}+\text{K}]^+$ , 26 %).

d. 1,3-Di(hydroxyacetyl-amino)-2,4,6-triiodoacetophenone

1,3-Di(acetoxycetyl-amino)-2,4,6-triiodoacetophenone (0.171 g, 0.23 mmol) was dissolved in a mixture of methanol (30 ml) and water (5 ml) containing 2 M aqueous NaOH (3 ml). The solution was stirred for 90 min and was then neutralized using a strongly acidic cation exchange resin. The solvents were removed by evaporation and the residue was purified by preparative HPLC. Yield: 98 mg (54 %).

30 MS (ESP, m/e): 644 ( $\text{M}^+$ , 100 %), 666 ( $[\text{M}+\text{Na}]^+$ , 95 %).

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Example 22. 3,5-Di(hydroxyacetyl-amino)-1-hydroxyacetyl-2,4,6-triiodobenzene

5 a. 3,5-Di(acetoxyacetyl-amino)-1-bromoacetyl-2,4,6-triiodobenzene

1,3-Di(acetoxyacetyl-amino)-2,4,6-triiodoacetophenone (0.20 g, 0.279 mmol) was dissolved in glacial acetic acid and bromine (0.044 g, 0.28 mmol) was added. The  
10 reaction was stirred at 2.5 h at 75 °C and then allowed to cool. The solvents were removed by evaporation and the residue was used directly in the next step.  
MS (ESP, m/e): 806 (M<sup>+</sup>, 100 %), 808 (M<sup>+</sup>, 98 %).

15 b. 3,5-Di(acetoxyacetyl-amino)-1-acetoxyacetyl-2,4,6-triiodobenzene

3,5-Di(acetoxyacetyl-amino)-1-bromoacetyl-2,4,6-triiodobenzene (10 mg, 0.12 mmol) was converted into the  
20 corresponding acetate by heating to 110 °C in glacial acetic acid (5 ml) containing sodium acetate (1 mmol) and AgOCOCF<sub>3</sub> (0.11 g, 0.5 mmol) for 16 h. The product was purified by preparative HPLC. The yield was not determined.  
25 MS (ESP, m/e): 786 (M<sup>+</sup>, 100 %).

c. 3,5-Di(hydroxyacetyl-amino)-1-hydroxyacetyl-2,4,6-triiodobenzene

30 Hydrolysis of 3,5-di(acetoxyacetyl-amino)-1-acetoxyacetyl-2,4,6-triiodobenzene was carried out analogous to Example 4e. The crude product was purified by preparative HPLC. The yield was not determined.  
MS (ESP, m/e): 687 ([M+HCOOH]<sup>+</sup>, 100 %).

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Example 23. 3,5-Di(hydroxyacetyl-amino)-1-(1,2-dihydroxyethyl)-2,4,6-triiodobenzene

a. 3,5-Dinitrophenylethanol

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3,5-Dinitroacetophenone (3.27 g, 0.0156 mol) was dissolved in a mixture of absolute ethanol (75 ml) and THF (37.5 ml) and the mixture was cooled to -10 °C. NaBH<sub>4</sub> (0.30 g, 7.9 mmol) was added and the mixture was stirred for 1 h at -10 °C. Water (80 ml) and ethyl acetate were added, the phases were separated and the organic phase was washed with water (80 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed by evaporation and the residue was purified by chromatography on neutral alumina using a mixture of pentane and ethyl acetate (1:1) as the eluent. Yield: 2.52 g (76 %).

10

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.95 (t, J=2.0 Hz, 1H), 8.60 (d, J=2.0 Hz, 1H), 8.59 (d, J=2.0 Hz, 1H), 5.15 (q, J=7.5 Hz, 1H), 1.61 (d, J= 7.5 Hz, 3H).

20

b. 3,5-Dinitrostyrene

3,5-Dinitrophenylethanol (1.0 g, 4.7 mmol) was mixed with P<sub>2</sub>O<sub>5</sub> (1.0 g, 0.71 mmol) and the stirred mixture was heated to 100 °C. After 3 h, the mixture was allowed to cool to room temperature and water (0.4 ml) was added. The pH was adjusted to 9 using 1 M aqueous NaOH and extracted with diethyl ether (2x25 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude product was used without further purification in the next step.

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<sup>1</sup>H NMR CDCl<sub>3</sub>): 8.92 (t, J=2.0 Hz, 1H), 8.56 (d, J=2.0 Hz, 2H), 6.86 (dd, J<sub>1</sub>= 18.4 Hz, J<sub>2</sub>=10.9 Hz, 1H), 6.08 (d, J=18.0 Hz, 1H), 5.67 (d, J=10.9 Hz, 1H).

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c. 1-(1,2-Dihydroxyethyl)-3,5-dinitrobenzene

3,5-Dinitrostyrene (0.50 g, 2.58 mmol) was dissolved in a mixture of acetone and water (8:1, 70 ml) and the solution was cooled to 0 °C. OsO<sub>4</sub> (0.046 g, 0.18 mmol) and NMO (0.60 g, 5.15 mmol) were added and the solution was stirred at room temperature for 16 h. A solution of Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (1.5 g) in water (120 ml) was added and the organic solvent removed by evaporation. The aqueous phase was extracted with ethyl acetate (2x70 ml) and the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The product was purified by preparative HPLC. Yield: 0.44 g (75 %).

<sup>1</sup>H NMR (CD<sub>3</sub>CN): 8.87 (t, J=2.0 Hz, 1H), 8.63 (t, J=2.0 Hz, 2H), 4.98 (t, J=6.0 Hz, 1H), 3.64-3.79 (m, 2H), 2.34 (s, 2H).

MS (ESP<sup>-</sup>, m/e): 227 (M<sup>-</sup>, 50 %), 197 ([M-CH<sub>2</sub>O]<sup>-</sup>, 100 %).

d. 1-(1,2-Dihydroxyethyl)-3,5-diaminobenzene

1-(1,2-Dihydroxyethyl)-3,5-dinitrobenzene (0.10 g, 0.44 mmol) was dissolved in methanol (35 ml) and hydrogenation was carried out at 60 psi using a Pd/C catalyst (10 %, 50 mg). The catalyst was filtered off and the solution was evaporated. Yield: 0.074 g (100 %).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): 6.14 (d, J=2.0 Hz, 2H), 6.06 (t, J=2.0 Hz, 1H), 4.98 (br s, 6H), 4.43-4.50 (m, 1H), 3.52-3.57 (m, 2H).

MS (ESP, m/e): 170 (M<sup>+</sup>, 100 %), 210 ([M+K]<sup>+</sup>, 18 %).

e. 1-(1,2-Dihydroxyethyl)-3,5-diamino-2,4,6-triiodobenzene

1-(1,2-Dihydroxyethyl)-3,5-diaminobenzene (0.0584 g, 0.242 mmol) was dissolved in a mixture of methanol (5 ml) and aqueous 2 M HCl (1.2 ml) and a solution of KICl<sub>2</sub> (70 % in water, 0.97 mmol) was added in one portion.

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After stirring for 20 min at room temperature, a 10 % aqueous NaHSO<sub>3</sub> solution (0.2 ml) was added, the solvents were removed by evaporation and the residue was purified by preparative HPLC. Yield: 31.4 mg (24 %).

5    <sup>1</sup>H NMR (CD<sub>3</sub>OD): 5.56-5.63 (m, 1H), 4.03-4.12 (m, 1H), 3.79-3.87 (m, 1H), 5.06 (br s, 4H).

f. 1-(1,2-Dihydroxyethyl)-3,5-di(hydroxyacetylamino)-2,4,6-triiodobenzene

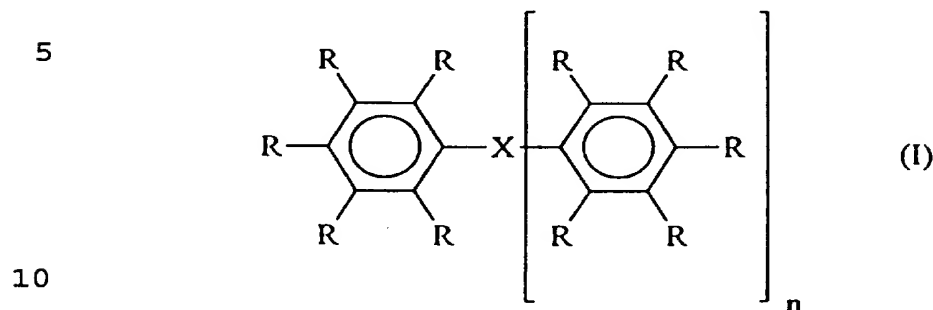
10

1-(1,2-Dihydroxyethyl)-3,5-diamino-2,4,6-triiodobenzene is acylated with acetoxyacetyl chloride using for example such a procedure as described in Example 4d. The crude product is then hydrolyzed analogous to Example 4e to give the final product. Purification of the crude product is carried out using preparative HPLC.

15

Claims

## 1. Compounds of formula I



(wherein  $n$  is 0 or 1, and where  $n$  is 1 each  $C_6R_5$  moiety may be the same or different; each group  $R$  is a hydrogen atom, an iodine atom or a hydrophilic moiety  $M$  or  $M_1$ , two or three non-adjacent  $R$  groups in each  $C_6R_5$  moiety being iodine and at least one  $R$  group in each  $C_6R_5$  moiety being  $M$  or  $M_1$  moieties;  $X$  denotes a bond or a group providing a 1 to 7 atom chain linking two  $C_6R_5$  moieties or, where  $n$  is 0,  $X$  denotes a group  $R$ ; each  $M$  independently is a non-ionic hydrophilic moiety; and each  $M_1$  independently represents a  $C_{1-4}$ alkyl group substituted by at least one hydroxyl group and optionally linked to the phenyl ring via a carbonyl, sulphone or sulfoxide group, at least one  $R$  group being an  $M_1$  moiety; with the proviso that where  $n$  is zero either at least one  $M_1$  group other than a hydroxymethyl or 1,2-dihydroxyethyl group is present or then if one hydroxymethyl or 1,2-dihydroxyethyl  $M_1$  group is present at least one nitrogen-attached hydroxylated alkyl moiety-containing  $M$  group is also present) and isomers thereof.

2. Compounds as claimed in claim 1 wherein  $n$  is 1.

3. Compounds as claimed in claim 2 wherein at least one  $R$  group in each  $C_6R_5$  moiety is an  $M_1$  moiety.

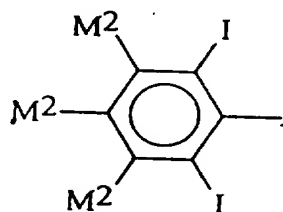
- 46 -

4. Compounds as claimed in claim 2 wherein X is an asymmetric group.

5. Compounds as claimed in claim 2 wherein the two  $C_6R_5$  groups are different.

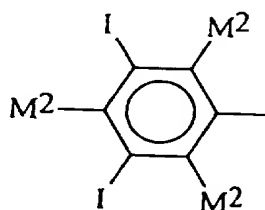
6. Compounds as claimed in claim 1 wherein n is zero and the phenyl ring is asymmetrically substituted.

7. Compounds as claimed in claim 2 wherein one  $C_6R_5$  group is of formula



where each  $M^2$  independently is a group M or  $M^1$ .

8. Compounds as claimed in claim 2 wherein one  $C_6R_5$  group is of formula

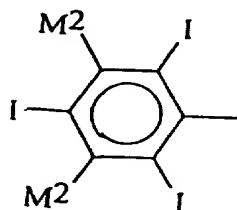


where each  $M^2$  independently is a group M or  $M^1$ .

9. Compounds as claimed in claim 2 wherein each  $C_6R_5$  group is of formula



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5

where each M<sup>2</sup> independently is a group M or M<sup>1</sup>.

10

10. Compounds as claimed in claim 1 wherein the M groups are straight chain or branched C<sub>1-10</sub>-alkyl groups with one or more CH<sub>2</sub> or CH moieties replaced by oxygen or nitrogen atoms or substituted by one or more groups selected from oxo, hydroxy, amino, carboxyl derivative, and oxo substituted sulphur and phosphorus atoms.

15

11. Compounds as claimed in claim 1 wherein the M groups are groups selected from

20

-CONH-CH<sub>2</sub>CH<sub>2</sub>OH,

-CONH-CH<sub>2</sub>CHOHCH<sub>2</sub>OH,

-CONH-CH(CH<sub>2</sub>OH)<sub>2</sub>,

-CON(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>,

25

-CONH<sub>2</sub>,

-CONHCH<sub>3</sub>,

-OCOCH<sub>3</sub>,

-N(COCH<sub>3</sub>)H,

-N(COCH<sub>3</sub>)C<sub>1-3</sub>-alkyl,

30

-N(COCH<sub>3</sub>)-mono, bis or tris-hydroxy C<sub>1-4</sub>-alkyl,

-N(COCH<sub>2</sub>OH)-mono, bis or tris-hydroxy C<sub>1-4</sub>-alkyl,

-N(COCH<sub>2</sub>OH)<sub>2</sub>,

-CON(CH<sub>2</sub>CHOHCH<sub>2</sub>OH)(CH<sub>2</sub>CH<sub>2</sub>OH),

-CONH-C(CH<sub>2</sub>OH)<sub>3</sub> and

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-CONH-CH(CH<sub>2</sub>OH)(CHOHCH<sub>2</sub>OH).

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12. Compounds as claimed in claim 1 wherein the  $M_1$  groups are selected from  $C_{1-4}$ -alkyl groups substituted by 1, 2, 3 or 4 hydroxy groups and optionally connected to the phenyl ring via a CO, SO or  $SO_2$  group.

5

13. Compounds as claimed in claim 1 wherein the  $M_1$  groups are selected from hydroxymethyl, 2-hydroxyethyl, 2,3-bishydroxy-propyl, 1,3-bishydroxyprop-2-yl, 2,3,4-trihydroxybutyl, 1,2,4-trihydroxybut-2-yl,  $COCH_2OH$  and  $SO_2CH_2OH$ .

10

14. Compounds as claimed in claim 1 wherein n is 1 and X is a bond, an oxygen atom or a group  $NR^1$ , CO,  $SO_2$ ,  $CR_2^1$ , COCO,  $CONR^1$ ,  $COCR_2^1$ ,  $SOCR_2^1$ ,  $SO_2NR^1$ ,  $CR_2^1CR_2^1$ ,  $CR_2^1NR^1$ ,  $CR^1_2O$ ,  $NR^1CONR^1$ ,  $ONR^1$ ,  $CONR^1CO$ ,  $CONR^1CR^1_2$ ,  $OCOO$ ,  $CR^1_2OCR^1_2$ ,  $OCR^1_2CO$ ,  $CR^1_2CONR^1$ ,  $CR^1_2CR^1_2CR^1_2$ ,  $COCR^1R^1CO$ ,  $CR^1_2NR^1CR^1_2$ ,  $CR^1_2SO_2NR^1$ ,  $CR^1_2OCO$  or  $NR^1SO_2NR^1$ , where  $R^1$  is hydrogen or a  $C_{1-6}$ -alkyl or alkoxy group optionally substituted by hydroxy, alkoxy, oxa or oxo and where it is attached to a carbon atom  $R^1$  may also be a hydroxyl group.

15

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15. Compounds as claimed in claim 1 wherein n is 1 and X is  $-NR^1COCONR^1-$ ,  $-NR^1COCR^1_2CONR^1-$ ,  $-NR^1CR^1_2CR^1OHCR^1_2NR^1-$ ,  $-CONR^1CR^1_2CONR^1-$ , or  $-N(COR^1)CR^1_2CR^1OHN(COR^1)-$  where  $R^1$  is as defined in claim 14.

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16. A diagnostic composition comprising a compound of formula I as defined in any preceding claim together with at least one physiologically tolerable carrier or excipient.

30

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/02265

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C237/46 C07C235/16 C07C275/42 A61K49/04 C07C33/48  
C07C33/46

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,23 17 535 (BRACCO IND CHIMICA SPA) 30 May 1974 see claims; examples ---	1-16
A	WO,A,88 09328 (BRACCO IND CHIMICA SPA) 1 December 1988 see page 1 - page 2 -----	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

18 December 1995

Date of mailing of the international search report

- 4. 01. 96

Name and mailing address of the ISA

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Authorized officer

Pauwels, G

# INTERNATIONAL SEARCH REPORT

I national application No.

PCT/GB95/02265

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
The expression "non-ionic hydrophilic moiety" used in claim 1 is ambiguous and therefore obscure. For purposes of the search an aromatic HO-group has been considered as an ionic hydrophilic group.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/02265

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2317535	30-05-74	CH-A- 576255 FR-A- 2258844 GB-A- 1375139	15-06-76 22-08-75 27-11-74
WO-A-8809328	01-12-88	AU-B- 618535 CA-A- 1327600 DE-A- 3873766 EP-A, B 0365541 IE-B- 63232 IL-A- 86450 JP-T- 2503556 US-A- 5066823 ZA-A- 8803610	02-01-92 08-03-94 17-09-92 02-05-90 05-04-95 30-05-94 25-10-90 19-11-91 28-11-88